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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/015,551	12/11/2001	Keith D. Allen	R-227	4290

7590 06/17/2003

DELTAGEN, INC.
740 Bay Road
Redwood City, CA 94063

EXAMINER
NGUYEN, QUANG

ART UNIT	PAPER NUMBER
1636	8

DATE MAILED: 06/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/015,551	ALLEN, KEITH D.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) *13,14,16,27-29,31 and 32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,15,17-26 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-32 are pending in the present application.

Applicant elected with traverse the invention of Group II (claims 1-12, 15, 17-26 and 30) in Paper No. 7 is acknowledged.

Applicant argues basically that the Examiner has not established that a serious burden would result from a search of the invention groups together, and that the subject matter of each of the invention groups is related; e.g., disruption in a brain-specific membrane-anchored protein gene in a mouse would reveal results that would encompass the subject matter of each group and therefore it would not be a serious burden to the examiner for searches and examination. Applicants' arguments are respectfully found to be unpersuasive because the inventions are distinct for the reasons already set forth in the previous Office Action in Paper No. 6. Also, the search and examination for a transgenic mouse with a disruption in a brain-specific membrane-anchored protein (BSMAP) gene is not the same or coextensive with the inventions involving an agonist or antagonist of a BSMAP receptor, an agent identified by the screening methods of the present invention, or phenotypic data of the present invention in a database. Furthermore, Applicant is entitled for a single patentable invention per patent application. This is made FINAL.

Accordingly, claims 13-14, 16, 27-29 and 31-32 are withdrawn from further consideration because they are drawn to non-elected inventions.

Claims 1-12, 15, 17-26 and 30 are examined on the merits herein.

Claim Objections

Claim 1 is objected to because the abbreviation BSMAP is not spelled out at the first occurrence of the term. Appropriate correction is required.

Claims 5-7 are objected to because of the following informalities: the claims encompass non-elected embodiments, e.g., cells comprising a disruption in a BSMAP gene that are not necessarily derived from a non-human transgenic animal. Appropriate correction is required.

Claim Rejections - 35 USC § 101

Claims 1-12, 15, 17-26 and 30 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either an asserted utility which is **specific and substantial,** or a well established utility.

The invention is drawn to a construct targeting a brain-specific membrane-anchored protein (BSMAP) gene; a method for producing the same targeting construct, a non-human transgenic animal comprising a disruption in a BSMAP gene as well as a cell derived from the same non-human transgenic animal, a method for making the same non-human transgenic animal, and methods for identifying an agent that modulates the function or the expression of a BSMAP gene or ameliorates a phenotype associated with a disruption in a BSMAP gene using the same non-human transgenic animal. The specification teaches by exemplification the preparation of a transgenic mouse whose genome comprises a homozygous disruption of the BSMAP gene, wherein the transgenic mouse displays supposedly an increased Prepulsed inhibition,

particularly with a 100 dB prepulse in comparison with the age- and gender matched wild-type control mouse (page 51, lines 29-31). However, upon examination of Figure 3, the only relevant data provided by the instant specification, the observed difference in Prepulsed inhibition between the transgenic mouse comprising a homozygous disruption of the BSMAP gene and the wild-type control mouse is not statistically significant (please note that the error bars of the Prepulse inhibition values for the control wild-type mouse extend to and include the mean Prepulse inhibition values for the transgenic knockout mouse). Therefore, there is no apparent significant difference or obvious difference in the phenotype between a wild-type control mouse and a transgenic mouse comprising a homozygous disruption of the BSMAP gene. It is also noted that the Prepulse inhibition test only reflects one component of the startle reflex. At the effective filing date of the present application, little is known about the physiological role or function of the BSMAP gene. Elson et al. (Biochem. Biophys. Res. Commun. 264:55-62, 1999; IDS) have identified the BSMAP gene to be localized on human chromosome 19p12, and speculate that due its highly preferential expression in the brain the BSMAP may have a role in brain function. Elson et al. further state "We failed to identify any genetic disease implicating CNS function which have been mapped to this precise region of chromosome 19." (page 55, col. 2, second last sentence). Because the defined function for the BSMAP or its gene is not known and is not taught in the specification, the invention has no utility which is **specific** and **substantial** at the effective filing date of the present application. The speculation that BSMAP may play a

generic role in brain function is not deemed to be a specific and substantial utility for this novel BSMAP.

The specification asserts a variety of utilities for the claimed invention, including uses of the cell-and animal-based systems of the present invention as models for diseases, for identifying compounds that ameliorate disease symptoms, for production of antibodies, for identifying agents that modulate the expression or the function of the BSMAP gene. However, such uses would require the determination of the physiological function or role of the BSMAP gene and its gene product, and in the absence of such guidance provided by the instant specification and in the prior art, they do not constitute a substantial utility at the effective filing date of the present application. A substantial utility is a utility which defines a "real world" use. Utilities which require further research to identify or confirm a real world use are not substantial utilities. For the reasons set forth above, a skilled artisan would not be able to use the presently claimed invention for any substantial purpose without further research and experimentation.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-12, 15, 17-26 and 30 are rejected under 35 U.S.C. 112, first paragraph. Because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility for the reasons set forth above under 35

U.S.C. 101, one skilled in the art would not know how to use the claimed invention at the effective filing date of the present application.

Should Applicant overcome the Utility rejection, the specification is still not enabled for the present broadly claimed invention for the following reasons.

(1) The breadth of the claims. The instant claims encompass a construct targeting a BSMAP gene derived from any animal species, a method for producing the same targeting construct, any non-human transgenic animal including a transgenic mouse comprising a disruption in a BSMAP gene having any phenotype including stimulus processing abnormality or prepulse inhibition abnormality, a cell derived from the same transgenic animal, a method of producing a transgenic mouse comprising a disruption in a BSMAP gene by introducing the targeting construct of the present invention into any cell, and methods for identifying an agent that modulates the expression or the function of a BSMAP gene or ameliorates a phenotype associated with a disruption in a BSMAP gene using the non-human transgenic animal of the present invention.

(2) The state and unpredictability of the prior art. At the effective filing date of the present application, Elson et al. (Biochem. Biophys. Res. Commun. 264:55-62, 1999; IDS) have identified the BSMAP gene to be localized on human chromosome 19p12, and speculate that due its highly preferential expression in the brain the BSMAP may have a role in brain function. Elson et al. further state "We failed to identify any genetic disease implicating CNS function which have been mapped to this precise region of

chromosome 19." (page 55, col. 2, second last sentence). In effect, little is known about the physiological role or function for BSMAP gene and its gene product. Additionally, apart from the mouse flanking genomic sequences disclosed in the present application, the genomic sequences of BSMAP genes derived from animal species other than a human are not known in the art (Elson et al., Biochem. Biophys. Res. Commun. 264:55-62, 1999; IDS).

At the effective filing date of the present application, the art of transgenic knockout is highly unpredictable. Particularly, the predictability of an anticipated phenotype arises from the disruption of a particular gene. Moreadith et al. (J. Mol. Med. 75:208-216, 1997) supported phenotypic unpredictability in knockout mice. In particular, Moreadith et al. discussed that gene targeting at a particular locus is unpredictable with respect to the resulting phenotype since often the generation of knockout mice, in many instances, changes the prevailing notions regarding the functions of the encoded proteins. For example, Moreadith et al. reported that gene targeting at the endothelial loci led to the creation of mice with Hirschsprung's disease instead of the anticipated phenotype of abnormal control of blood pressure (See page 208, column 2, second paragraph). It is also well known in the transgenic knockout art that the production of knockout animals other than mice is undeveloped. This is because the ES cell technology is generally limited to the mouse system, at present, and that only "putative" ES cells exist for other species (Moreadith et al., Summary on page 214). Seamark (Reprod. Fertil. Dev. 6:653-657, 1994) supported this observation by reporting that totipotency for ES cell technology in many livestock species has not

been demonstrated (see abstract). Likewise, Mullins et al. (J. Clin. Invest. 98:S37-S40, 1996) stated "although to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell has been successfully demonstrated" (column 1, first paragraph, page S38).

(3) The amount of direction or guidance provided. Apart from the disclosure of a transgenic mouse whose genome comprises a homozygous disruption of the BSMAP gene, exhibiting an increased Prepulsed inhibition with a 100 dB prepulse that is not statistically significant (see Figure 3) in comparison with the age- and gender matched wild-type control mouse, the specification fails to describe any other non-human transgenic animals having a disruption in their BSMAP genes, and that they display any relevant phenotype. It is also noted that the Prepulse inhibition test only reflects one component of the startle reflex, and it is not a representative test for evaluating stimulus processing abnormality in general. The instant disclosure also fails to provide any guidance for a skilled artisan on how to make a transgenic mouse comprising a disruption of a BSMAP gene by introducing the gene targeting construct into any cells (other than mouse embryonic stem cells), let alone for the construction of any non-human transgenic animal as claimed. Nor does the specification provide guidance for a skilled artisan on how to make or obtain any ES cell derived from non-mouse species for the making and using of the broadly claimed non-human transgenic animals. It is also unclear on the basis of the present disclosure, how can one **use** a transgenic mouse or a non-human transgenic animal comprising a heterologous disruption of the

BSMAP gene without any phenotype distinguishable from a wild-type mouse? Similarly, it is unclear how cells obtained from any non-human transgenic animal of the presently claimed invention that do not possess any phenotype can be used and for what purposes. As enablement requires the specification to teach how to **make and use** the claimed invention, given the lack of sufficient teachings provided by the present application and in light of the state of the art and the unpredictability of the art as a whole, particularly the unpredictability associated with the attainment of any desired phenotype in any animal species as a result of a disruption or knockout of a target gene, it would have required undue experimentation for a skilled artisan **to make and use** the instant claims.

With regard to the breadth of the instant claims for any non-human transgenic animal, any BSMAP gene, any desired phenotype, Applicants' attention is further directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

Additionally, the courts have also stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in the patent application (27 USPQ2d 1662 *Ex parte Maizel.*).

Accordingly, due to the lack of guidance provided by the specification regarding to the issues raised above, the unpredictability of the transgenic art as well as the art on

the novel BSMAP gene, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to **make and use** the presently claimed invention.

Written Description

Claims 1-5, 8-9, 11-12 and 15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed. "Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

Applicant's invention is drawn to a targeting construct specifically for a brain-specific membrane-anchored protein (BSMAP) gene derived from any animal species; a method for producing such a gene targeting construct, any non-human transgenic animal comprising a disruption in a BSMAP gene and a cell derived from the same non-human transgenic animal, as well as methods for identifying an agent that modulates the function or the expression of a BSMAP gene using the same non-human transgenic

animal. Apart from the disclosure of a transgenic mouse whose genome comprises a homozygous disruption of the BSMAP gene, exhibiting an increased Prepulsed inhibition with a 100 dB prepulse that is not statistically significant (see Figure 3) in comparison with the age- and gender matched wild-type control mouse, the specification fails to describe any other non-human transgenic animals having a disruption in their BSMAP genes. Nor do Applicant provides any information regarding to the genomic sequences of BSMAP genes derived from animal species other than a human known in the art (Elson et al., Biochem. Biophys. Res. Commun. 264: 55-62, 1999; IDS) and the mouse flanking genomic sequences. As such, the instant specification fails to provide sufficient written description for BSMAP genes derived from any non-human animals for the preparation of BSMAP gene targeting constructs, non-human transgenic animals comprising a disruption in a BSMAP gene and cells derived thereof and methods of screening an agent using the same as encompassed within the scope of the presently claimed invention. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). Apart from a transgenic mouse whose genome comprises a homozygous disruption of the BSMAP gene, exhibiting an increased Prepulsed inhibition with a 100 dB prepulse that is not statistically significant in comparison with the age- and gender matched wild-type control mouse, and a targeting construct used to construct such a transgenic mouse,

the skilled artisan cannot envision the detailed structure of a targeting construct, a non-human transgenic animal, a cell derived from the same transgenic animal and methods of using the same as broadly claimed by the present invention, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10 and 21-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 10, 21 and dependent claims of claim 21, in step (b), the term "the cell" is unclear. Is it the cell of step (a) containing the BSMAP gene targeting construct or a cell used in step (a) without the gene targeting construct? Clarification is requested because the metes and bounds of the claims are not clearly determined.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gerald Leffers, Jr., Ph.D., may be reached at (703) 305-6232, or SPE, Remy Yucel, Ph.D., at (703) 305-1998.

Quang Nguyen, Ph.D.

PATENT EXAMINER
A.U. 1636